The European Research Journal 2022;8(1):31-36 Original Article

DOI: 10.18621/eurj.822127 *Infectious Diseases and Clinical Microbiology*

The response to double-dose hepatitis B vaccination in patients with HIV

Melda Türken[1], Tuba Tatlı Kış[2], Sabri Atalay[1], Şükran Köse[1]

[1]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, İzmir Tepecik Training and Research Hospital, İzmir, Turkey
[2]Department of Infectious Diseases and Clinical Microbiology, Şırnak Silopi State Hospital, Şırnak, Turkey

ABSTRACT

Objectives: Prevention of hepatitis B virus (HBV) infection is necessary for patients with human immunodeficiency virus (HIV), since co-infection is associated with increased in mortality. The aim of this study was to investigate response to double-dose HBV vaccine in patients with HIV.

Methods: A total of 149 patients with HIV were retrospectively evaluated. Sixty-eight patients who were HBV seronegative and administered double-dose HBV vaccine were included in the study. According to anti HBs levels, patients were evaluated in three groups: < 10 mIU/mL, 10-100 mIU/mL and ≥ 100 mIU/mL. Age, sex, transmission route, smoking, alcohol-substance abuse, comorbidities, CD4+ T cells counts and HIV viral load were compared in three groups.

Results: The rate of response to HBV vaccination (anti HBs ≥ 10 mIU/mL) was 69.1%. Age was statistically significantly higher in the anti HBs < 100 mIU/mL group than in the anti HBs >100 mIU/mL group. The level of anti HBs was statistically significantly lower in patients with a CD4+ T cell count < 200 cells/μL (< 100 mIU/mL).

Conclusions: The use of high-dose vaccine is a necessity as well as revaccination to improve vaccine immunogenicity in patients with HIV. In our study, low CD4+ T lymphocyte count and older age were found to have a negative effect on vaccine response.

Keywords: HIV, HBV, co-infection, HBV vaccination, response

Patients with human immunodeficiency virus (HIV) infection are frequently coinfected with hepatitis B virus (HBV) because routes of transmission are shared [1]. Some 30%-90% of patients with HIV have serologic finding of previous HBV infection, and 10% have CHB infection. Co-infection with HIV and HBV was associated with an eight-fold increase in mortality compared with HIV monoinfection [2]. Therefore, prevention of HBV infection and HBV vaccination are necessary for patients with HIV. However, response rates to standard hepatitis B vaccination for patients with HIV are 24%-56%, compared with > 90% for immunocompetent hosts [3, 4].

The response to the HBV vaccine is influenced by the CD4+ T cell count and level of viral load. According to international guidelines; in patients with low CD4+ T lymphocyte counts (< 200 cells/μL) and high viral load, antiretroviral treatment (ART) should be initiated before HBV vaccination [5]. In patients who are HIV positive and who were vaccinated for HBV

***Received:** November 5, 2020; **Accepted:** July 26, 2021; **Published Online:** Januar 4, 2022*

***How to cite this article:** Türken M, Tatlı Kış T, Atalay S, Köse Ş. The response to double-dose hepatitis B vaccination in patients with HIV. Eur Res J 2022;8(1):31-36. DOI: 10.18621/eurj.822127*

***Address for correspondence:** Melda Türken, MD., University of Health Sciences, İzmir Tepecik Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, 35120 Yenişehir, İzmir, Turkey. E-mail: meldaulusoy@gmail.com, Tel: +90 232 4696969, GSM: +90-505 6731125, Fax: +90 232 4330756*

e-ISSN: 2149-3189

and do not respond [hepatitis B surface antibody (anti HBs) < 10 IU/L], revaccination should be considered. Double dose (40 µg) at 3-4 time points (0, 1, 6, and 12 mounts) may help to increase response rates to the HBV vaccine [5, 6].

The aim of this study was to investigate the rate of response to double-dose HBV vaccine and to compare the affecting factors to response in patients with HIV.

METHODS

The local ethics committee in Izmir Tepecik Training and Research Hospital approved the study. The study was designed as retrospective, observational. A total of 149 patients who were admitted to Tepecik Training and Research Hospital HIV/AIDS outpatient clinic between 2004 and 2017 and who were aged over 18 years and were HIV positive were evaluated for this study. Patients who were not adherent and were not followed up regularly (n = 20), who had natural immunity against HBV (n = 32), a previous response with HBV vaccine (n = 12), those who were HBsAg positive (n = 4) and, isolated hepatitis B core antigen (anti HBc) IgG positive (n = 13) were excluded from the study. Sixty-eight patients who were HBV seronegative (HBsAg negative, anti HBs negative, anti HBc IgG negative) were included in the study.

The patients' age, sex, HIV transmission route, smoking and alcohol-substance abuse status, comorbid diseases, CD4+ T cells counts and, viral load (HIV RNA) levels were recorded to assess the impact on vaccine response. HBsAg, anti HBc IgG and antiHBs results were tested by on enzyme-linked immunosorbent assay (ELISA) (Liason, Diasorin Diagnostic Specialist S.T.A., Italy). After evaluation of viral load, CD4+ T lymphocyte count and hepatitis markers in patients, vaccination and antiretroviral therapy (ART) were started simultaneously for HBV-sensitive patients.

Double-dose (40 µg) hepatitis B vaccine [hepatitis B virus surface antigen (HBsAg) (recombinant) 20 µg / 1 dose (1 mL) of Euvax (BERK)] was administered to 68 patients who were HBV seronegative at 0, 1 and 6 months. AntiHBs levels were assessed 6-8 weeks after the last vaccine. According to the antiHBs levels, patients were evaluated in 3 groups: < 10 mIU/mL (Group 1), 10-100 mIU/mL (Group 2) ve and ≥ 100 mIU/mL (Group 3). Those with an antiHBs level < 10 mIU/mL were considered as non-responsive to the first vaccination. Patients who did not respond to the first vaccination program were again vaccinated with double-dose (40 µg) hepatitis B vaccine at 0, 1, and 6 months.

Statistical Analysis

The data were evaluated using the IBM SPSS Statistics 22.0 statistical package program (IBM Corp., Armonk, New York, USA). Descriptive statistics are given as unit number (n), percentage (%), mean ± standard deviation (SD), median and interquartile range (IQR). Pearson's Chi-square test and Fisher's exact test were used to evaluate the categorical variables. The normal distribution of the numerical variables was evaluated using the Shapiro-Wilk test, the normality test, and Q-Q graphs. The independent sample t-test was used to compare two groups with normal distribution and the Mann-Whitney U test was used for groups with the non-normal distribution. In the comparison of three or more groups, one-way analysis variance (ANOVA) was used for normally distributed variables, and Kruskal-Wallis analysis was used for non-normally distributied variables. In multiple comparisons, Tukey's honestly significant difference (HSD) test was used for normal dividing variables and Dunn-Bonferroni test was used for normal non-dividing variables. A p value of < 0.05 was considered statistically significant.

RESULTS

The HBV serology of total 149 patients with HIV was evaluated (Table 1). The mean age of the patients was 52 (range,19-85) years. One hundred twenty-four patients (83.2%) were male. In the study, 37.98% (n = 49) patients with HIV had evidence of prior HBV infection, and 3.10% (n = 4) had chronic infection (HBsAg seropositive). At 0, 1, and 6 months, double-dose (40 µg) recombinant HBV vaccine was administered in all HBV-seronegative patients with HIV. Antibody levels were assessed at 6-8 weeks after the end of the vaccination programme. According to the anti HBs levels, 21 patients with < 10 mIU/mL (Group 1), 22 patients with 10-100 mIU/mL (Group 2), and 25 patients with ≥ 100 mIU/mL (Group 3) were iden-

Table 1. HBV serology in patients with HIV

HBV serology	Patients number n (%)
HbsAg (+)	4 (3.10)
Immunity against HBV infection HbsAg (-), AntiHBs (+), antiHbcIgG (+)	32 (24.80)
Isolated anti HBcIgG (+) HBsAg (-), Ant iHBs (-), antiHbcIgG (+)	13 (10.07)
Previously response of HBV vaccine HBsAg(-), Anti HBs (+), antiHbcIgG (-)	12 (9.30)
Seronegative HBsAg (-), anti HBs (-), anti HBcIgG (-)	68 (52.71)
Unfollow-up patients	20 (13.42)
All patients	149 (100)

tified. A total of 47 patients (69.1%) with anti HBs titers ≥ 10 mIU/mL were evaluated as vaccinated.

Ten of 21 patients who did not respond to the vaccine (anti HBs titers < 10 mIU/mL) received a double-dose of 0, 1, 6. month (40 µg) hepatitis B vaccination program second time. In three of these patients (30%), a response to the vaccine was achieved. The response to HBV vaccination in patients with HIV is shown in Table 2.

Age, sex, HIV transmission route, smoking-alcohol-substance abuse, comorbidities, CD4+ T cells counts, and HIV viral load results are shown in Table 3.

The age factor was statistically significant between group 1 and 2 and between group 1 and 3. (respectively $p = 0.038$, $p = 0.022$).

In patients with CD4+ T lymphocyte counts < 200 cells/µL, the level of antiHBs was found to be significantly lower (< 100 mIU/mL) than in patients with more than 200 cells/uL. ($p = 0.045$). Response of antiHBs antibody according to CD4+ The T lymphocyte counts are shown in Table 4.

In this study, age and CD4+ T cell counts were found significant factors in terms of response to hepatitis B vaccination in patients with HIV ($p < 0.05$).

Table 2. Response to HBV vaccination in patients with HIV

Vaccinated patients (n)	68
Responders, n (%)	47 (69.11)
Non-responders, n (%)	21 (30.88)
Vaccinated patients at second times (n)	10
Responders, n (%)	3 (30.00)
Non-reponders, n (%)	7 (70.00)
Non vaccinated patients at second times (n)	11

DISCUSSION

HIV affects the course of HBV infection negatively. HBV infection is a vaccine-preventable disease and although hepatitis B vaccination has a lower response rate, all HIV-infected patients are recommended to be vaccinated [7-10].

The risk of chronicity for HBV infection increases in patients with HIV who are HBSAg positive. Chronic hepatitis B (CHB) infection is around 5-10% in patients with HIV. Co-infected patients have a higher progression to cirrhosis and liver cancer and higher mortality than patients with a monoinfection. [6, 11, 12].

With the development of highly active antiretroviral treatment (HAART) and with better survival rates, liver disease has become a leading cause of mortality and is of great concern in co-infected patients with HIV-HBV. The incidence of acute HBV infection is lower among such patients than in patients infected with HBV alone however chronic HBV infection occurs more often [13-15]. In our study, 37.98% (n = 49) of patients with HIV had evidence of prior HBV infection, and 3.1% (n = 4) had chronic infections (HbsAg seropositive). The seropositivity rate of HBsAg in the patients with HIV was lower than in the literature [2, 11]. In addition, 9.3% of our patients were pre-vaccinated. Routine vaccination started in 1998 in our country and therefore these findings in the study were thought to be related to the predominance of the middle age group.

The effect of the vaccination program in Turkey that initiated in 1998 was observed decrease of HBsAg seroprevalence over time. In a previous review, HBsAg seroprevalence in Turkey was reported to be between 2.5-9%. This rate is 3.1% in patients with HIV. In another multi-center study, HBsAg seroprevalence was reported as 6.2% in HIV patients. In a study

Table 3. Anti HBs levels according to risk factors

Anti HBs levels	< 10 mIU/mL	10-100 mIU/mL	≥ 100 mIU/mL	*p value*
Patients (n)	21	22	25	
Age (years)*	46.45 ± 14.749[a]	47.09 ± 18.163[b]	35.56 ± 9.648[c]	**ac = 0.038 bc = 0.022**
Male gender	17	15	20	0.536
MSM	6	4	8	0.960
CD4 counts**	435 (410.75)	504.5 (562.75)	629 (602.5)	0.580
Viral load**	75500 (265650)	79838 (140499.5)	61700 (102550)	0.900
Smokers	12	12	12	0.722
Alcohol users	8	8	10	0.960
Narcotic drug users	3	1	2	0.485
DM	1	1	1	0,986
Comorbidities	5	6	5	0.841

*Mean ± standard deviation, **Median (IQR), MSM: Men who have sex with men, DM = Diabetes mellitus

Table 4. Response of anti HBs antibody according to CD4+ T lymphocyte counts

		CD+ T lymphosyties counts (cells/µl)		Total
		< 200	**≥ 200**	
AntiHBs (mIU/mL)	**< 100**	13	30	43
	≥1 00	2	23	25
Total		14	53	68

p = 0.045

by Inci *et al*., HBsAg positivity was 4.4%; exposure to hepatitis B (antiHBc IgG) was 34%. [16-18]. All these data point to the risk of co-infection in patients with HIV and emphasize the importance of vaccination in newly diagnosed young adults.

In general, symptomatic HIV-infected patients have suboptimal immunologic responses to vaccines. The antibody response to the antigen used in HBV vaccines, HBsAg, has been previously shown to be T-cell dependent, to induce a suboptimal antibody titer more frequently in HIV-positive individuals, and to more rapidly decline to non-protective levels than in HIV-negative controls [19].

In international guidelines, vaccination is preferably recommended after suppressed viremia and immune reconstitution (CD4+ T cell counts > 200 /µL). It is recommended to measure anti-HBs titers to evaluate their efficacy because vaccine responses can be significantly lower in patients with HIV [5]. Data on vaccination in isolated anti HBc IgG positive patients are not sufficient. For this reason, there is no clear recommendation for these patients. In patients at risk for HBV, if antibody response does not develop after HBV vaccination, annual HBV serology should be followed [5]. ART regimens containing tenofovir alafenamide or tenofovir disoproxil fumarate (TAF/TDF) are recommended for these patients. Revaccination is recommended until reaching anti HBs antibodies of ≥10 mIU/mL / ≥100 IU/L according to national guidelines [5]. In particular, in patients with low CD4 count and high viral load, who do not respond to HBV vaccine, double-dose (40 µg) vaccination is recommended 3 times if the antibody level is under 10 mIU / mL and once if it is under 100 mIU / mL [5]. In our study, the vaccine response was 30% in patients who were did not respond to the first vaccination program (anti HBs < 10 mIU/mL) and these patients were then vaccinated for a second time.

Response to HBV vaccine achieves in 80-90% of healthy adults. Antibody level > 10 mIU/mL is considered unresponsive. Antibody levels > 100 IU/L are regarded as ideal [20]. Age over 40 years, male sex,

obesity, hemodialysis, smoking, and being immunocompromised, including through HIV infection are factors that reduce responses to HBV vaccination [6]. After standard vaccination in patients with HIV, response rates to the vaccine range from 7% to 88% and are strongly correlated with CD4 cell numbers and viral load [23-29]. To improve the vaccine response, it is recommended that non-responders be re-vaccinated and use of higher and more frequent vaccine doses when viral load is suppressed with ART and CD4 + T lymphocyte counts are > 350-500 cells/μL [25-29].

In a systematic review and meta-analysis of five studies including a total of 883 patients, anti HBs response with high-dose (40μg) vs. standard-dose (20 or 10μg depending on vaccine type) vaccination were compared. It was observed that high dose vaccination increased the response rates [28]. In an open-label, multicenter, randomized study of patients with CD4 + T lymphocyte count > 200 cells/μL, three HBV vaccination strategies were evaluated. Three standard dose (20 μg) intramuscular administrations at 0, 1, and 6 months, four high-dose (40 μg) intramuscular administrations at 0, 1, 2, and 6 months, and four low-dose (4 μg) intradermal administrations at 0, 1, 2, and 6 months were compared. The response rates in patients were found 65%, 82%, 77%, respectively [28]. In another a cohort study authors reported that anti HBs response rates were 83% and 91% after three and four double-doses, respectively, and anti HBs levels were higher with the four-dose schedule [30]. In these studies, high-dose vaccination has been shown to increase response rates in nonresponders [28-30].

The main aim of this study was to investigate the results of high-dose vaccination and re-vaccination of non-responders to increase the HBV vaccine response in patients with HIV. There are similar studies in the literature. However, in our study, it is noteworthy that the double-dose vaccine was effective even though the patients had a high viral load. We think this is the reason for the initiation of ART in all patients. In addition, low CD4+ T lymphocyte count and older age were found to have a negative effect on vaccine response as in other studies. The rate of re-vaccination response was found as 30% in our study. These results also support the recommendations for re-vaccination in the guidelines.

CONCLUSION

In conclusion, the double-dose vaccination response in patients with HIV was consistent with the literature in this study. The use of high-dose vaccine is a necessity, as well as revaccination to improve vaccine immunogenicity in immunocompromised patients with HIV. The factors affecting response were found as age and CD4+ T lymphocyte counts, which were significantly different in the groups with anti HBs levels < 100 mIU/mL and ≥ 100 mIU/mL.

Authors' Contribution

Study Conception: MT, ŞK; Study Design: MT, TTK, SA; Supervision: MT, SA, ŞK; Funding: MT; Materials: MT, TTK; Data Collection and/or Processing: MT, TTK; Statistical Analysis and/or Data Interpretation: MT, TTK, SA; Literature Review: MT, SA; Manuscript Preparation: MT, TTK and Critical Review: MT, SA, ŞK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Acknowledgements

We thank Dr. Recep Balik from Tepecik Training and Research Hospital for helping in statistical analysis.

REFERENCES

1. Pasricha N, Datta U, Chawla Y, Singh S, Arora SK, Sud A, et al. Immune responses in patients with HIV infection after vaccination with recombinant Hepatitis B virus vaccine. BMC Infect Dis 2006; 6:65.
2. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, et al.; Multicenter AIDS Cohort Study. HIV-1, hepatitis B, and risk of liver-related mortality in the Multicenter AIDS Cohort Study (MACS). Lancet 2002;360:1921-6.
3. Overton ET, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. Clin Infect Dis 2005; 41:1045-3.
4. Van Herck K, Van Damme P, Thoelen S, Meheus A. Long-term

persistence of antiHBs after vaccination with a recombinant DBA yeast derived hepatitis B vaccine: 8 year results. Vaccine 1998;16:1933-5.
5. European AIDS Clinical Society Treatment Guidelines. Available at <http://www.eacsociety.org/files/guidelines_9.0-english.pdf > Accessed: October 2017.
6. British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. Available at <https://www.bhiva.org/vaccination-guidelines> Accessed: November 2015.
7. İnci A, Fincancı M. [Antibody response to a standard dose of hepatitis B vaccine in HIV-infected patients]. Klimik Journal 2014;27:12-4. [Article in Turkish]
8. Kellerman SE, Hanson DL, McNaghten AD, Fleming PL. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. J Infect Dis 2003;188:571-7.
9. Kim HN, Harrington RD, Crane HM, Dhanireddy S, Dellit TH, Spach DH. Hepatitis B vaccination in HIV-infected adults: current evidence, recommendations and practical considerations. Int J STD AIDS 2009;20:595-5.
10. Flynn PM, Cunningham CK, Rudy B, Wilson CM, Kapogiannis B, Worrell C, et al. Hepatitis B vaccination in HIV-infected youth: a randomized trial of three regimens. J Acquir Immune Defic Syndr 2011;56:325-7.
11. Colin JF, Cazals-Hatem D, Loriot MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology 1999;29:1306-4.
12. Martin-Carbonero L, Poveda E. Hepatitis B virus and HIV infection. Semin Liver Dis 2012;32:1149.
13. Thio CL. Hepatitis B in the human immunodeficiency virus-infected patient: epidemiology, natural history, and treatment. Semin Liver Dis 2003;23:125-11.
14. Bodsworth N, Cooper D, Donovan B. The influence of HIV-1 infectionon the development of hepatitis B virus carrier state. J Infect Dis 1991;163:1138-2.
15. Gilson RJ, Hawkins AE, Beecham MR, Ross E, Waite J, Briggs M, et al. Interactions between HIV and hepatitis B in homosexual men: effects on the natural history of infection. AIDS 1997;11:597-606.
16. Atalay S, Kış TT, Sönmez U, Köse Ş. Hepatitis B and C seroprevalence in patients with human immunodeficiency virus/acquired immune deficiency syndrome at tertiary care hospital in Izmir. Viral Hepat J 2018;24:3-6.
17. Hahné SJ, Veldhuijzen IK, Wiessing L, Lim TA, Salminen M, Laar Mv. Infection with hepatitis B and C virus in Europe: a systematic review of prevalence and cost-effectiveness of screening. BMC Infect Dis 2013;13:181.
18. İnci A, Fincancı M, Soysal F. HIV/HBV co-infected cases. J Clin Anal Med 2015;6:439-3.
19. Wong E, Bodsworth NJ, Slade MA, Mulhall BP, Donovan B. Response to hepatitis B vaccination in a primary care setting: influence of HIV infection, CD4+ lymphocyte count and vaccination schedule. Int J STD AIDS 1996;7:490-4.
20. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis 1999;179:489-3.
21. Cornejo-Juárez P, Volkow-Fernández P, Escobedo-López K, Vilar-Compte D, Ruiz-Palacios G, Soto-Ramírez LE. Randomized controlled trial of Hepatitis B virus vaccine in HIV-1-infected patients comparing two different doses. AIDS Res Ther 2006;3:9.
22. Tedaldi EM, Baker RK, Moorman AC Wood KC, Fuhrer J, McCabe RE, et al. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. Clin Infect Dis 2004;38:1478-6.
23. Rey D, Krantz V, Partisani M, Schmitt MP, Meyer P, Libbrecht E, et al. Increasing the number of hepatitis B injections augments antiHBs response rate in HIV infected patients. Effect on viral load. Vaccine 2000;18:1161-5.
24. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV infected adult patients comparing a standard dose to a double dose. Vaccine 2005;23:2902-8.
25. Hoebe CJ, Vermeiren AP, Dukers-Muijrers NH. Revaccination with Fendrix® or HBVaxPro® results in better response rates than does revaccination with three doses of Engerix-B® in previous nonresponders. Vaccine 2012;30:6734-7.
26. Launay O, van der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs Standard hepatitis B vaccine regimen in adults with HIV−1: a randomized controlled trial. JAMA 2011;305:1432-40.
27. Whitaker JA, Rouphael NG, Edupuganti S, Lai L, Mulligan MJ. Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV−1. Lancet Infect Dis 2012;12:966-10.
28. Ni JD, Xiong YZ, Wang XJ, Xiu LC. Does increased hepatitis B vaccination dose lead to a better immune response in HIV−infected patients than standard dose vaccination: a meta analysis. Int J STD AIDS 2013;24:117-5.
29. De Vries−Sluijs TE, Hansen BE, van Doornum GJ, Springeling T, Evertsz NM, de Man RA, et al. A prospective open study of the efficacy of high−dose recombinant hepatitis B rechallenge vaccination in HIV infected patients. J Infect Dis 2008;197:292-4.
30. Potsch DV, Oliveira ML, Ginuino C, Miguel JC, Oliveira SA, Silva EF, et al. High rates of serological response to a modified hepatitis B vaccination schedule in HIV-infected adults subjects. Vaccine 2010;28:1447-3.